Child abuse and recovery

Thomaes, K.

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Increased activation of the left hippocampus region in Complex PTSD during encoding and recognition of emotional words: a pilot study

Kathleen Thomaes, Ethy Dorrepaal, Nel Draijer, Michiel B de Ruiter, Bernet M Elzinga, Anton J van Balkom, Paulien LM Smoor, Johannes H Smit, Dick J Veltman. *Psychiatry Research: Neuroimaging, 2009, 171: 44-53.*

ABSTRACT

Objective: To gain insight into memory disturbances in Complex posttraumatic stress disorder (Complex PTSD) we investigated declarative memory function and medial temporal lobe activation in patients and non-trauma-exposed healthy controls.

Methods: A case-control study was performed in nine patients with Complex PTSD and nine controls. All respondents performed a declarative memory task with neutral and emotional, negative words during functional magnetic resonance imaging.

Results: Memory performance of neutral words was impaired in Complex PTSD with a relative conservation of recall of negative words. Deep encoding of later remembered negative words as well as correct recognition of negative words and false alarms were associated with an enhanced Blood Oxygenation Level Dependent response in the left hippocampus extending into the parahippocampal gyrus of Complex PTSD patients compared with controls. Post-hoc volumetric comparisons did not reveal significant anatomical differences in the medial temporal lobe between Complex PTSD patients and controls.

Conclusion: We conclude that in Complex PTSD preferential recall of negative words is associated with increased activation in the left hippocampus and parahippocampal gyrus during both successful and false recall. These findings support a model of an abnormally functioning hippocampus in Complex PTSD.

INTRODUCTION

Sexual and physical child abuse appears to be a crucial etiological factor in the development of several psychiatric disorders such as posttraumatic stress disorder (PTSD). Sexual abuse affects 10% of Dutch women (Draijer, 1990; Kessler et al., 1995). The risk of PTSD following exposure to any type of trauma is 10 to 20% with the highest risk associated with assaultive violence (Breslau et al., 1998). Terr (Terr, 1991) divides trauma into two basic types: Type I trauma refers to a single non-interpersonal traumatic event; type II trauma refers to repeated and interpersonal traumatic events, such as child abuse. More severe symptoms are associated with type II trauma (Green et al., 2000). After type II trauma 'simple' PTSD (re-experiencing, numbing and hyper arousal) can be complicated by additional features such as impaired affect regulation, dissociation and memory disturbances, disturbances of self-image and relational problems (Herman, 1992; Van Der Kolk et al., 1996; Zlotnick et al., 1996). This syndrome has been brought under the heading of 'PTSD with associated features' in DSM-IV-TR (APA, 2000) or 'Disorders of Extreme Stress Not Otherwise Specified' (DESNOS) and is also known by clinicians as 'Complex PTSD'. In a student population prevalence of Complex PTSD was found to be 1% (Ford et al., 2006). It is associated with severe psychiatric symptoms, high co-morbidity and social maladjustment and tends to run a chronic course in spite of considerable use of medical and psychiatric services (Höing, 2003).

Memory dysfunction is a central feature of PTSD. On the one hand, memories of traumatic events can be intrusive in PTSD patients, as in flashbacks and nightmares, disturbing normal daily activities. On the other hand, memory fails during periods of numbing and dissociation. In several neuropsychological studies PTSD has been associated with impaired performance on memory tests (Sutker et al., 1992; Vasterling et al., 1998) with a preference for remembrance of trauma related material compared with neutral material (Chemtob et al., 1999; McNally, 2006).

Animal studies have shown that stress, particularly early in life, during a 'window of susceptibility' may have profound and enduring effects on the regulation of stress later in life. A history of child abuse is related to increased neuro-endocrine stress reactivity, which is further enhanced when additional trauma is experienced in adulthood (Heim et al., 2002). Early adverse events are associated with structural and functional changes in brain areas involved in emotion processing and long-term declarative memory functioning, especially parts of the medial temporal lobe (MTL) such as the amygdala, the hippocampus and the

parahippocampal gyrus (Elzinga & Bremner, 2002; Sapolsky, 2000). The hippocampus is a key structure associated with declarative memory function and receives extensive inputs from brain regions involved in emotion processing (Rolls & Kesner, 2006).

A meta-analysis on 21 structural imaging studies (Karl et al., 2006) revealed a significantly smaller volume of the right and left hippocampus in adult subjects with (chronic) PTSD compared with both trauma-exposed and non-trauma-exposed controls without PTSD. Stronger effect sizes were found in male versus female PTSD patients. Moreover, effect sizes increased with PTSD severity. Effect sizes increased with age as well, but in older patients with PTSD a smaller hippocampal volume has not been found (Freeman et al., 2006; Golier et al., 2005; Yehuda et al., 2007). So, not all magnetic resonance imaging studies on chronic PTSD revealed a decreased hippocampal volume; negative results have been reported both with manually segmentation methods and automated techniques (Jatzko et al., 2006).

Smaller hippocampal volumes have been found in patients with major depressive disorders (MDD) as well, especially associated with repeated episodes (Videbech & Ravnkilde, 2004). However, a study with a specific comparison of MDD patients with child abuse versus non-trauma-exposed MDD patients found volume losses exclusively in the trauma-exposed group (Vythilingam et al., 2002). Furthermore, hippocampal volumes appeared to be smaller in patients with - trauma related - dissociative identity disorder (DID) as well (Ehling et al., 2007; Vermetten et al., 2006) and in trauma-exposed borderline patients (Driessen et al., 2000). So, we may conclude that a smaller hippocampus may not be specific for PTSD; nevertheless it has been found especially in psychiatric disorders related to early trauma.

Functional imaging studies have shown conflicting results with regard to the hippocampus in PTSD (Francati et al., 2007). Blood flow in the hippocampus was found to be diminished during retrieval of negative word pairs in female PTSD patients with child sexual abuse histories (n = 10) compared with non-trauma-exposed controls (n = 11) (Bremner et al., 2003b) and during encoding of a (neutral) paragraph in women with child sexual abuse and PTSD (n = 10) compared with abused controls without PTSD (n = 12), suggesting that hippocampal dysfunction is related to the diagnosis of PTSD and not to the abuse itself (Bremner et al., 2003a). In line with these findings, intrusive memories of child sexual abuse were associated with decreased blood flow in the right hippocampus in women with PTSD (n = 10) relative to abused women without PTSD (n = 12) (Bremner et al., 1999a). Decreased hippocampal function was also found

using the hippocampus-dependent virtual Morris water task during functional MRI (fMRI) in PTSD patients (Astur et al., 2006). In contrast, increased perfusion of the left hippocampus was found during recall of (shallowly encoded) neutral words in type I PTSD patients (n = 8) compared with trauma-exposed controls without PTSD (n = 8)(Shin et al., 2004b). And in an earlier study of Shin et al (Shin et al., 2001) an increased hippocampus activation was also found in PTSD patients performing a counting Stroop task with trauma related, general negative and neutral words. In patients with MDD an increased activation in the hippocampus has also been found (Videbech et al., 2002), but not consistently (Bremner et al., 2004b). Also at the level of the parahippocampal gyrus conflicting results have emerged: increased activation during active trauma recall in type II trauma related PTSD (Bremner et al., 1999a; Driessen et al., 2004) and decreased activation in type I PTSD patients (Lanius et al., 2003).

Summarizing, impaired memory function and related brain changes have been found in different types of PTSD. However, empirical data have been sparse and contradictory. Moreover, it is unclear whether the investigated samples included patients that met criteria for Complex PTSD. The aim of the present study was to investigate the neurophysiologic correlates of memory in patients with Complex PTSD. To this end, we assessed regional perfusion differences (using fMRI) during performance of a verbal episodic memory task, with neutral as well as trauma related words. We compared both performance (reaction times and error rates) and perfusion changes, particularly in the medial temporal lobe (MTL) between subjects with Complex PTSD and normal controls. Hypotheses were: 1) that Complex PTSD patients perform worse during a verbal declarative memory task with a preference for negative words relative to neutral words, and 2) that this is reflected by a difference in Blood Oxygenation Level Dependent (BOLD) response in the hippocampus and parahippocampal gyrus between patients and controls.

METHODS

Subjects

Nine female patients with both PTSD and Complex PTSD after child sexual and/or physical abuse and nine female non-trauma-exposed healthy controls participated in the study. All patients were recruited by clinical referral and were interviewed with the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I) (First et al., 1995), the Structured Clinical Interview for Disorders of Extreme Stress (SIDES)(Van der Kolk et al., 1992) and the Structured Trauma Interview (STI)(Draijer N, 1989). In line with the STI, sexual abuse was defined as

repeated, forced sexual contact with a perpetrator in an intimate relationship; physical abuse as severely repeated maltreatment such as confinement, battering and being pushed from the stairs.

Exclusion criteria were recurrent psychoses; antisocial personality disorder according to the SIDP-IV (Pfohl, 1997); dissociative identity disorder (DID) according to the SCID-D (Steinberg et al., 1990); the use of psychotropic medication other than selective serotonin reuptake inhibitors (SSRI) in stable dosage; major neurological and internal disorders affecting neuro-endocrine function. Further exclusion criteria for MRI were: retained metal (e.g., surgical clips or pacemaker) and pregnancy. Out of 22 patients, seven were excluded due to the use of tricyclic antidepressant or antipsychotic drugs, one due to a history of cocaine addiction while five refused to participate because of fear for the scanning procedure, resulting in nine included patients. Eight patients were free of psychotropic medication; one patient had a stable dose of a fluoxetine 40 mg.

Symptom severity was measured with the Davidson Trauma Scale (DTS) (Davidson et al., 1997), Dissociative Experiences Scale (DES)(Bernstein & Putnam, 1986), Beck Depression Inventory (BDI) (Beck et al., 1998) and Symptom Checklist - 90 (SCL-90) (Derogatis et al., 1973). Female controls matched on age were recruited via advertisements in local newspapers. The Medical Ethical Committee of the VU University Medical Center, Amsterdam, approved of the present study. Written informed consent was obtained from each participant.

Stimuli and activation paradigm

The verbal declarative memory task with neutral (e.g. chair, table) and negative (e.g. torture, rape) words used in the present study was adapted from de Ruiter et al (de Ruiter et al., 2007). Participants were asked to indicate the level of subjective distress on a scale of 0 (no distress) to 100 (extreme distress) at four time points during the MRI-session. During the encoding phase, stimuli were presented in an event-related design, consisting of two randomized series of 80 words (40 neutral and 40 negative). In the shallow encoding condition, subjects were requested to make alphabetical judgments ("Are the underlined letters alphabetically ascending or descending?"). For deep encoding a semantic classification instruction was used addressing the personal meaning of the word ("Do you think the word has a neutral or negative meaning?"). Subjects were asked to respond as fast as possible by pressing a button.
After a structural MRI had been performed, 240 words were presented in random order to test recognition (40 neutral and 40 negative shallowly encoded words, 40 neutral and 40 negative deeply encoded words, 40 new neutral and 40 new negative words). During the recognition task, subjects were asked to rate each

word as (i) novel, (ii) probably seen before, or (iii) certainly seen before. Because subjects hardly used the "probably seen" option, these responses were pooled with the "certainly seen" category for analysis. During both encoding tasks and recognition task, 40 baseline stimuli were presented randomly ("Push left" or "Push right button", and in recognition also "Push middle button").

Scanning procedures

Functional MR imaging was performed on a 1.5-T Sonata MR system (Siemens, Erlangen, Germany) with a standard head coil at the VU University Medical Center. Stimuli were projected on a screen at the end of the scanner table, which was seen through a mirror mounted above the subject's head. One magnet-compatible 4-key response button box was used to record the subject's performance and response times (RT). To reduce motion artifacts, the subject's head was immobilized using foam pads.

During each scanning session, T2*-weighted echo-planar images sensitive to BOLD contrast covering the medial temporal lobe (14 coronal slices, between-plane resolution 5 mm, in-plane resolution 3x3 mm; TR 1.45 - 1.50 s, TE 45 ms) were acquired while subjects performed each task. In addition, a coronal T1-weighted MR image (matrix = 256 x 256, voxel size = 1 x 1 x 1.5 mm, 160 slices) was performed for anatomical overlays of T2*-weighted images. Each MRI session lasted about 40 minutes.

Data analysis

Demographic data were normally distributed; an independent t-test has been used to test whether controls were well matched on these variables. Clinical status variables did not have a normal distribution; therefore, non-parametric tests (Mann-Whitney) were applied to test differences between means. Main outcome measures were: 1) task performance on a declarative memory task with neutral and negative words during f-MRI and 2) BOLD response in the MTL during functional MRI.

Task performance (error rates and reaction times) was assessed by analyses of variance (ANOVA) with GROUP (Patients-Controls) x TASK (Deep-Shallow encoded words) x VALENCE (Neutral-Negative words) interactions. Because performance on the shallow encoding task was worse for the clinical group compared with the control group, performance on this task was correlated with years of education of respondents (ANCOVA). Group effects and interactions were thus corrected for this variable. In case of significant interactions post-hoc tests were performed.

Subjects' responses during performance of the memory task allowed post-hoc classification of events in correctly remembered (hits), correctly rejected words and false alarms, so as to correlate them separately with functional imaging data. Functional imaging data were analyzed with SPM2 (www.fil.ion.ucl.ac.uk/spm, Welcome Department of Imaging Neuroscience, Institute of Neurology, University College of London). Functional images were reoriented, realigned, and the mean image was co-registered with a whole-brain image. Spatial normalization into approximate Talairach and Tournoux space was performed using a standard SPM echo planar-imaging template. For spatial smoothing a 6 mm FWHM filter was used. Data were analyzed in the context of the general linear model, using delta functions convolved with a canonical hemodynamic response to model responses during each condition. The resulting contrast images containing parameter estimates for main effects were entered into a second-level (random effects) analysis, using one-way analyses of variance (ANOVAs) for each contrast. Uncorrected p-values were justified because of clear hypotheses and a restricted scan area. Main effects are reported at an uncorrected $p < 0.001$ and Group interactions at an uncorrected $p < 0.005$, unless indicated otherwise. In addition, post-hoc volumetric comparisons were performed using Voxel-Based Morphometry as implemented in SPM5, also using a threshold of an uncorrected $p < 0.001$ (Ashburner & Friston, 2000).

RESULTS

Subjects

In Table 1 demographic and clinical status variables are shown. All subjects were female by inclusion and right handed. Controls were significantly higher educated than included patients (Table 1: independent t-test t = -2.9, df = 15, p < 0.05). All patients had experienced child physical abuse (n = 9) and the majority (n = 7) had also experienced child sexual abuse. Age of abuse was before age 12 except for one between 12 and 16 years. Furthermore, it turned out that all patients had also experienced physical (n = 2) or sexual abuse (n = 1) or both (n = 6) as adults. Controls had experienced no sexual or physical abuse or other traumatic experiences.

Table 1: Demographic and clinical status variables of included subjects (all female, all right handed): means (standard deviations)

	Patients with Complex PTSD (n = 9)	**Healthy controls (n = 8)**
	Mean (SD)	Mean (SD)
Age	30.6 (6.0)	32.9 (9.3)
Years of education	9.0 (2.4)	12.1 (2.0) *
Number of axis I diagnoses (DSM-IV-TR)	3.3 (0.9)	0
Number of axis II diagnosis (DSM-IV-TR)	1.6 (2.3)	0
Symptom severity		
DTS	88.9 (33.5) **	1.3 (2.4)
DES	38.1 (11.9) **	3.6 (4.1)
BDI	31.5 (11.4) **	1.5 (2.5)
SCL-90	276.6 (73.2) **	101.8 (7.7)

DTS = Davidson Trauma Scale (range 0 - 136; > 40 indicates PTSD); DES = Dissociative Experiences Scale (range 0 – 100, > 25 indicative for dissociative disorder NOS); BDI = Beck Depression Inventory (range 0 - 63; > 30 indicates severe depressive disorder); SCL-90 = Symptom Checklist -90 items (minimum score 90).

* Significantly different from Complex PTSD (independent t-test, controls > patients, p < 0.05).

** Significantly different from non-trauma-exposed healthy controls (Mann-Whitney U-test, patients > controls, p <0.001).

All patients met criteria for Complex PTSD (SIDES) and for PTSD (SCID-I) by inclusion. Patients had on average 3.3 (± 0.9) Axis-I diagnoses (DSM-IV-TR). Seven out of nine patients met criteria for current depressive disorder, one for lifetime depressive disorder; one patient for dysthymia; four for panic disorder (two with agoraphobia); four for social phobia; one for generalized anxiety disorder; one for bulimia; one for eating disorder NAO; one for pain disorder and one for somatization disorder. One out of nine patients met criteria for alcohol dependence (five in remission); two for alcohol abuse (and one in remission); two for

cannabis dependence (three in remission, one for GHB addiction in remission). Patients had in average 1.6 (± 2.3; 1 missing) Axis-II diagnoses. Five out of eight patients met criteria for borderline personality disorder and three had traits of BPD (SIDP-IV).

Symptom scores from included patients indicated severe PTSD (DTS: 88.9 ± 33.5; cut-off score = 40 indicating PTSD), severe dissociative symptoms (DES: 38.1 ± 11.9) and severe depressive symptoms (BDI: 31.5 ± 11.4, cut-off for severe depressive disorder = 30). In the control group the scores of the controls on the DTS (1.3 ± 2.4), DES (3.6 ± 4.1), BDI (1.5 ± 2.5) and SCL-90 (101.8 ± 7.7; minimum score = 90) were low, confirming their psychological health. During MR imaging patients reported significantly more subjective distress than controls (main effect GROUP: $F(1,15) = 10.2$, $p < 0.01$). Distress decreased in time in both patients and controls (main effect TIME: $F(1,3) = 11.4$, $p < 0.001$; TIME x GROUP interaction: $F(1,3) = 0.88$, $p = 0.46$).

Declarative memory task performance

In Table 2 percentage hits, false alarms, net performance and response bias are shown. The total group (patients and controls together) generated more hits on deeply than on shallowly encoded words (TASK $F(1,15) = 96.42$, $p < 0.001$), demonstrating that the encoding manipulation was successful. The total group also generated more hits on negative than on neutral words (VALENCE $F(1,15) = 22.37$, $p < 0.001$). Patients generated less hits than controls (main effect GROUP corrected for years of education: $F(1,14) = 18.27$, $p = 0.001$). This effect could be mainly explained by the fact that patients generated less hits on (deep) neutral words compared with controls (Table 2: 0.67 vs. 0.87, post-hoc ANOVA $F(1,15) = 8.86$, $p < 0.05$), with a relative conservation of hits on negative words (Table 2: 0.89 vs. 0.95, post-hoc ANOVA $F(1,15) = 1.53$, $p = 0.24$), confirming the expected valence effect.

The total group generated also more false alarms on negative than on neutral words (VALENCE: $F(1,15) = 10.38$, $p < 0.01$). Patients made less false alarms than controls (main effect GROUP corrected for years of education: $F(1,14) = 27.64$, $p < 0.001$) and had a more cautious response bias than controls (main effect for GROUP corrected for years of education: $F(1,14) = 33.52$, $p < 0.001$).

The total group's net memory performance (hits minus false alarms) was better in deeply than in shallowly encoded words (main effect TASK: $F(1,15) = 96.42$, $p < 0.001$). A TASK x GROUP interaction ($F(1,15) = 8.07$, $p < 0.05$; corrected for years of education: $F(1,14) = 1.91$, $p = 0.19$) indicated that although patients' net performance was about equal on shallowly encoded words, their net memory

performance on deeply encoded words was slightly better than in controls. Post-hoc analysis for deeply and shallowly encoded words separately however failed to reach significant effects (Table 2: Deep 0.51 and 0.48 vs. 0.39 and 0.36, post-hoc main effect for GROUP corrected for years of education: $F(1,15) = 2.73$, $p = 0.12$; Shallow 0.11 and 0.19 vs. 0.18 and 0.19: $F(1,14) = 0.01$, $p = 0.94$).

Table 2: Mean proportions (standard deviation) of percentage hits, false alarms, net performance and response bias for patients and controls for different word valences

Group	Patients		Controls	
Word valence	Neutral	Negative	Neutral	Negative
Hits deep encoded words	0.67 (0.25)	0.89 (0.13)	0.87 (0.08)	0.95 (0.06)
Hits shallow encoded words	0.27 (0.12)	0.59 (0.21)	0.65 (0.13)	0.78 (0.14)
False alarms	0.16 (0.09)	0.40 (0.25)	0.48 (0.14)	0.59 (0.10)
Net performance deep	0.51 (0.20)	0.48 (0.21)	0.39 (0.12)	0.36 (0.07)
Net performance shallow	0.11 (0.09)	0.19 (0.19)	0.18 (0.15)	0.19 (0.11)
Response bias deep	0.40 (0.31)	0.76 (0.23)	0.78 (0.15)	0.91 (0.09)
Response bias shallow	0.18 (0.10)	0.48 (0.23)	0.58 (0.13)	0.74 (0.13)

Hits = correctly recognized words, False alarms = falsely "recognized" new words, Net performance = hits minus false alarms, Response bias = tendency to respond in one direction; low bias indicates a cautious tendency i.e. the tendency to give 'not seen' responses.

BOLD response during deep encoding and recognition in Complex PTSD patients versus controls

BOLD responses are only reported for deeply encoded words. Because net performance on shallowly encoded words was poor (Table 2: 0.11 to 0.19), too few trials remained to correlate these with imaging data. Results for imaging data during encoding are listed in Table 3. The contrast of successfully remembered neutral words versus baseline showed an increased activation of the parahippocampal gyrus in both patients and controls (Table 3: main effect, no group interactions). Patients - but not controls - activated the hippocampus during encoding of neutral words versus baseline. However, the difference between groups was not statistically significant.

The contrast of remembered negative words versus baseline revealed a significantly enhanced BOLD response in the left hippocampus, extending into the parahippocampal and fusiform gyrus in patients (Table 3: main effect). Figure 1 illustrates that patients had also an increased BOLD response in this area when compared to controls (Table 3: group interactions).

Table 3: BOLD response in the medial temporal lobe during encoding of later remembered words (main effect per group and group interactions for each contrast)

Contrast	Group	Location	x, y, z (MNI)	Z
Deep neutral vs. baseline	Patients	L HC	-18,-12,-18	3.23
		L PHG	-36,-27,-21	2.72 [a]
	Controls	L PHG	-36,-24,-21	2.91 [a]
	Pa > Co	-	-	-
Deep negative vs. baseline	Patients	L PHG	-42, -30, -21	4.30
		L FG	-45, -36, -15	3.71
		L FG	-42, -42, -21	3.51
		L HC	-36, -15, -18	2.62 [a]
	Controls	-	-	-
	Pa > Co	L PHG/FG	-39, -27, -24	3.59
		L FG	-42, -39, -15	3.56
Deep negative vs. neutral	-	-	-	-

FG = fusiform gyrus; HC = hippocampus; PHG = parahippocampal gyrus ; x, y, z (MNI) = Montreal Neurologic Institute coordinates.
Main effects in the medial temporal lobe were reported at an uncorrected $p < 0.001$ except were indicated.
[a] $p < 0.005$.
Group interactions (Pa > Co): uncorrected $p < 0.005$.

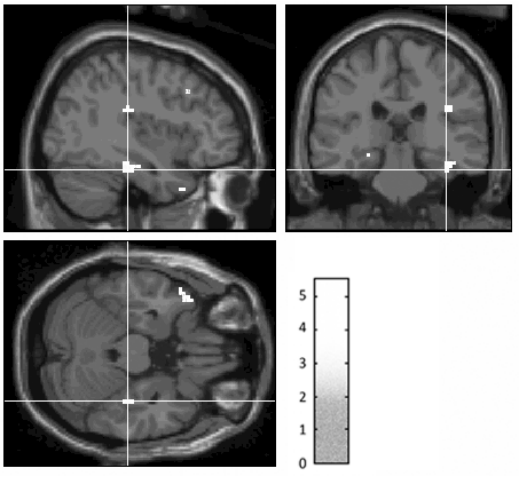

Figure 1: Increased BOLD response in the left parahippocampal gyrus extending to the hippocampus and fusiform gyrus in patients versus controls during encoding of – later remembered – negative words.

Results for imaging data during recognition are listed in Table 4. Hits on negative words compared to baseline were associated with an enhanced BOLD response in the left hippocampus and parahippocampal gyrus/entorhinal cortex in patients (main effect) and similarly when compared with controls (group interactions). Hits on neutral words were not associated with an increased BOLD response. Correctly rejected words (Table 4) compared with baseline were not associated with any difference in BOLD response in the MTL.

False alarms (negative and neutral words pooled) compared to baseline were also associated with an increased BOLD response in the left hippocampus of patients compared to controls (Table 4). There were not enough trials of false alarms on neutral words in patients (see Table 2: 0.16) to test valence effects for false alarms.

Hippocampus volumes measured by voxel-based morphometry (VBM)

Patients had smaller overall gray matter volumes (625 cm^3 ± 47) than controls (705 cm^3 ± 53) (independent t-test $t = 3.27$, $df = 15$, $p < 0.005$). We failed to observe volumetric differences in bilateral medial temporal lobe between patients and controls at our a priori threshold.

Table 4: BOLD response in the medial temporal lobe during recognition of deeply encoded words (main effect per group and group interactions for each contrast)

Contrast	Group	Location	x, y, z (MNI)	Z
Hits deep neutral vs. baseline	-	-	-	-
Hits deep negative vs. baseline	Patients	L HC	-21, -12, -15	2.91 [a]
		L PHG/EC	-36, -9, -33	2.66 [a]
	Controls	-	-	-
	Pa > Co	L HC	-30, -18, -9	2.97
		L PHG/EC	-36, -9, -33	2.63
Hits deep negative vs. neutral	-	-	-	-
Correct rejected neutral vs. baseline	-	-	-	-
Correct rejected negative vs. baseline	-	-	-	-
False alarms (negative and neutral) vs. baseline	Patients	L HC	-33, -9, -15	3.64
	Controls	-	-	-
	Pa > Co	L HC	-33, -9, -18	2.89
False alarms neutral vs. baseline	Too few trials		-	-
False alarms negative vs. baseline	Patients	L HC	-30, -9, -12	3.87
	Controls	-	-	-
	Pa > Co	-	-	-

EC = entorhinal cortex, HC = hippocampus, PHG = parahippocampal gyrus, x, y, z (MNI) = Montreal Neurologic Institute coordinates.
Main effects in the medial temporal lobe reported at an uncorrected $p < 0.001$; except were indicated.
[a] $p < 0.005$.
Group interactions (Pa > Co) reported at an uncorrected $p < 0.005$.

DISCUSSION

In the present study Complex PTSD patients showed impaired declarative memory for neutral words with a preservation of memory of negative words. Specifically, net performance (hits minus false alarms) for deeply encoded words was not worse but slightly better in patients than in controls. In patients deep encoding of - later remembered - negative words was associated with an enhanced BOLD response in the left hippocampus, extending to the parahippocampal and fusiform gyrus. In addition, both correct recognition of deeply encoded negative words and false alarms were associated with increased activation in the left hippocampus.

Impaired memory of especially neutral words with relative preservation of negative words of Complex PTSD patients is in line with the literature on 'simple' PTSD. Improved memory for negative material in Complex PTSD may be explained by the salience of emotional stimuli, associated with enhanced memory consolidation (Wittmann et al., 2005). However, when memory was corrected for false alarms, patients had a slightly better net performance of deeply encoded words relative to controls. A possible explanation is the more conservative response strategy of the patients (less hits, but also less false alarms). Moreover, in PTSD memory is enhanced when cued (Jenkins et al., 1998), as was done in the present study. No previous declarative memory imaging study (Bremner et al., 2003b; Bremner et al., 2003a; Shin et al., 2004b) found any differences in memory performance between PTSD patients and controls, but these studies included trauma-exposed controls, analyzed correct hits only (and not false alarms), whereas Shin et al (2004) used only neutral stimuli.

In the present study, in patients relative to controls, a significantly enhanced BOLD response was found in the left hippocampus, extending into parahippocampal and fusiform gyrus during encoding and recall of negative words. This observation is at odds with previous findings in two PET studies with female patient population with type II trauma (Bremner et al., 2003b; Bremner et al., 2003a; Shin et al., 2004b). A likely explanation is that in PET imaging is restricted to block designs, in which all words - correctly remembered, correctly rejected and false alarms - are analyzed together. The present event-related fMRI study provided the possibility of post-hoc selection of trials for later remembered words, correctly rejected words and false alarms, of which only the first two (i.e., correctly recognized words and false alarms) were associated with the enhanced activation in the MTL. Our findings seem to be in line with the findings of Shin et al (2001, 2004) among firefighters. These authors, however, explained their finding of hyper-responsiveness of the left hippocampus in firefighters with PTSD as due to elevated perfusion during recall of shallowly encoded words, which is not in line with our data.

Emotional salience was found to modulate accurate retrieval and to be associated with activation in specific limbic regions (Kensinger & Schacter, 2005). Elevated activation in the left hippocampus region on negative stimuli in Complex PTSD fits in this model. However, the hyperactivation of this region in the present study was not only found during correct recall but also during false alarms. This is in agreement with a model of an abnormally functioning hippocampus in PTSD (Rauch et al., 2006). Voxel-based morphometry analysis failed to reveal a statistically significant smaller MTL volume in patients compared to control subjects, which may have been due to our small sample size.

Co-morbid depressive disorder as well as dissociative disorder is very common in child abuse related Complex PTSD and emphasizes the severity of the syndrome. As this was also the case in our sample, we could not differentiate between the effects of trauma, PTSD, depressive disorder and/or dissociative disorder. As was found in patients with PTSD, increased activation in the hippocampus has also been found in MDD (Videbech et al., 2002) however not consistently (Bremner et al., 2004b). Furthermore, hippocampal volume was correlated with severity of depressive symptoms in trauma-exposed borderline patients (Driessen et al., 2000) and with dissociation in type II PTSD patients (Stein et al., 1997) and DID patients (Ehling et al., 2007). So, even if hippocampal hyperactivation is not specific for the PTSD syndrome, it seems to be correlated with psychiatric syndromes related to early trauma and with the severity of these disorders.

The present study focused on the medial temporal lobe to increase statistical power, so that we may have missed group differences with regard to brain activation in cortical regions known to be relevant for verbal memory, in particular in the prefrontal cortex.

Other limitations are the small sample size and the differences in level of education between patients and controls for which we, however, attempted to control.

The clinical implication of this study is that excessive attention towards negative input and increased activation in the MTL is associated with decreased memory for neutral material. In further analyses we will study whether neutral material can be better recalled after successful psychotherapy and is associated with an enhanced activation in the hippocampus.